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Application No.: 10/805,788  
Declaration of Henry R. Costantino

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Steven C. Quay, et al.	Assignee: Natestch Pharmaceutical Company Inc. by Reel/Frame 014824/0710
Application No.: 10/805,788	
Filed: 03/22/2004	
Title: NASAL CALCITONIN FORMULATIONS CONTAINING CHLOROBUTANOL	Art Unit: 1654 Confirmation No. 9945
Attorney Docket No.: 03-04US	Examiner: Thomas S. Heard

DECLARATION OF HENRY R. COSTANTINO UNDER 37 C.F.R. § 1.132

I, Henry R. Costantino, declare as follows:

1. I am currently Vice President of Pharmaceutical Research and Development at Natestch Pharmaceutical Company, Inc., 3830 Monte Villa Parkway, Bothell, WA 98021, the assignee of the above-identified patent application.
2. I hold B.S. and M.S. degrees in Chemical Engineering from The Johns Hopkins University. I hold a Ph.D. in Chemical Engineering from the Massachusetts Institute of Technology.
3. I have about 12 years of industrial experience in research and development of pharmaceutical formulations. Including my academic career, I have about 18 years experience in research and development of pharmaceutical formulations.
4. I have reviewed antimicrobial effectiveness testing which was conducted by Natestch Pharmaceutical Company on calcitonin salmon nasal spray formulated with varying levels of chlorobutanol. Representative data from this study for which the chlorobutanol content ranged from 0.125% to 0.5% are presented in Table 1.

Table 1: Antimicrobial Effectiveness Testing for Calcitonin Salmon Nasal Spray

Chloro- butanol Conc. (% w/w)	AET Results (USP)	<i>P.aeruginosa</i>		<i>E. coli</i>		<i>S. aureus</i>		<i>C. albicans</i>		<i>A. niger</i>	
		Days		Days		Days		Days		Days	
		14	28	14	28	14	28	14	28	14	28
0.125	Pass	5.4	5.4	5.3	5.3	5.3	5.3	1.1	1.1	1.3	1.5
0.25	Pass	5.4	5.4	5.3	5.3	5.3	5.3	5.8	5.8	1.6	1.7
0.375	Pass	5.4	5.4	5.3	5.3	5.3	5.3	5.8	5.8	1.5	2.0
0.50	Pass	5.4	5.4	5.3	5.3	5.3	5.3	5.8	5.8	1.9	2.3
		NLT		NLT		NLT		NLT		NLT	
USP		2.0	No inc	2.0	No inc	2.0	No inc	No inc	No inc	No inc	No inc

5. The results in Table 1 of paragraph 4 showed that all test samples of calcitonin salmon nasal spray formulated with varying levels of chlorobutanol met the appropriate U.S. Pharmacopoeia specifications (UPS Chapter <51> Antimicrobial Effectiveness Testing) because: (i) the concentrations of *P. aeruginosa*, *E. coli* and *S. aureus* are reduced by no less than 2.0 logs (NLT 2.0) by the 14th day, and no increase occurred from 14 days to 28 days; and (ii) the concentrations of *C. albicans* and *A. niger* showed no increase up to the 14th day, and continued to show no increase from the 14th to the 28th day (with an allowance of  $\pm 0.5$  log).

6. In sum, the results in Table 1 of paragraph 4 showed that chlorobutanol at a concentration of 0.25% in a calcitonin solution was suitable to submit for passing of USP criteria for antimicrobial effectiveness testing.

7. U.S. Patent No. 5,759,565 states in column 2, lines 39-41 that "chlorobutanol at 0.6% in calcitonin nasal pharmaceutical compositions showed insufficient activity against the test fungus *Pen. steckii*."

8. I believe that the reference U.S. Patent No. 5,759,565 would have been understood by a person of ordinary skill in the art on its publication date of June 2, 1998 to have taught in column 2, lines 35-67 that chlorobutanol had been tested in some calcitonin nasal

pharmaceutical compositions, and was found in those compositions to have insufficient activity at a concentration of 0.6% against the well-known test microorganism *Pen. steckii*.

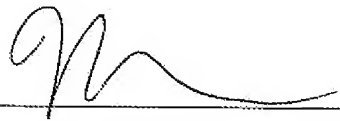
9. It is my opinion that a person of ordinary skill in the art in 1998 would have known in general that a preservative is less effective against microorganisms when used at a lower concentration.

10. It would therefore have been understood by a person of ordinary skill in the art in 1998 based on the teachings of the reference U.S. Patent No. 5,759,565 that it would have been doubtful that chlorobutanol could successfully be used at any concentration less than 0.6% as a preservative in a calcitonin nasal pharmaceutical composition.

11. I believe that the reference U.S. Patent No. 5,759,565 would have been understood by a person of ordinary skill in the art on its publication date of June 2, 1998 to have taught that an alternative preservative, namely benzalkonium chloride, was useful as a preservative in calcitonin nasal pharmaceutical compositions.

12. It is my opinion that the results in Table 1 of paragraph 4 showed that chlorobutanol at a concentration of 0.25% in a calcitonin salmon nasal spray was unexpectedly advantageous as a preservative in view of the teachings of the reference U.S. Patent No. 5,759,565 discussed in paragraphs 7-11.

Date: 24 Aug 07

  
Henry R. Costantino